4 5 6 7 8 9,
~~21, 22, 23, 24, 25~~ or ~~26,~~ [wherein E denotes an R_bNH-C(=NH)- group,] or a physiologically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.--

11
--~~29.~~ (amended) A method for [preventing or treating] the prophylaxis or treatment of venous and arterial thrombotic disease which comprises administering an antithrombotic amount of a compound according claim ~~18,~~ 1 wherein E denotes an R_bNH-C(=NH)- group, or a compound according to claim 2, 3, 4, 5, 6, 7, 8 9,
~~19, 20, 21, 22, 23, 24, 25~~ or ~~26,~~ [wherein E denotes an R_bNH-C(=NH)- group,] or a physiologically acceptable salt thereof.--

13
--~~31.~~ (amended) A method for providing antithrombotic support in thrombolytic treatment utilizing rt-PA or streptokinase, which comprises administering a therapeutically effective amount of a compound according claim ~~18,~~ 1 wherein E denotes an R_bNH-C(=NH)- group, or a compound according to claim 2, 3, 4, 5, 6, 7, 8 9,
~~19, 20, 21, 22, 23, 24, 25~~ or ~~26,~~ [wherein E denotes an R_bNH-C(=NH)- group,] or a physiologically acceptable salt thereof.--

Cancel claims 32 and 33.

REMARKS

Claims 18-33 were pending. Claims 27, 32 and 33 have been cancelled by amendment herein. Thus, claims 18, 19, 20, 21, 22, 23, 24, 25, 26, 28, 29, 30 and 31 are now pending.

Rejections under 35 U.S.C. §101 and §112 (first paragraph)

Claims 18-22 are rejected under 35 U.S.C. §101 and §112 (first paragraph). The specific ground given is that the phrase "and salts thereof", which appears at the ends of these claims, causes the claims to read on salts that are "too toxic for the intended medical purposes". The

action suggests that limiting the claims to the expression "or a physiologically acceptable salt thereof" would overcome the rejection.

In response to the the above-noted rejection, the Examiner is asked to note that claim 18 is directed to two kinds of compounds: intermediates (compounds wherein E is a cyano group) and final products (compounds wherein E is a group of the formula R_bNH-C-(=NH)-). Only the final products are intended for medicinal use. The applicants agree that the claims should not embrace physiologically unacceptable salts of the final products, as these would not be fit for the intended medicinal purposes. However, salts of the intermediate compounds need not be physiologically acceptable to be fit for their intended use (as intermediates for making the final products). Accordingly, claim 18 has been amended so that the phrase in question now reads as follows: "or, if E is a group of the formula R_bNH-C-(=NH)-, a physiologically acceptable salt thereof or, if E is a cyano group, a salt thereof." It is earnestly asserted that this amendment, which is partially in keeping with the suggestion made in the Action, overcomes the stated ground of rejection with respect to claim 18.

Claims 19-22, which are directed only to final products (compounds wherein E is a group of the formula R_bNH-C-(=NH)-) have been amended in the manner suggested in the action. That is to say, these claims as amended embrace only physiologically acceptable salts. Thus, claims 19-22 clearly avoid the stated ground of rejection.

Rejections under 35 U.S.C. §112 (second paragraph)

Claims 19-28 are rejected under 35 U.S.C. §112 (second paragraph) for several distinct reasons. Each such reason is discussed below.

1. Claims 19-22 depend from Claim 1

Claims 19-22 are rejected as improperly depending from claim 1, which has been cancelled. To overcome this ground of rejection, claims 19-22 have been amended in the manner suggested in the action, so that they now depend from claim 18.

2. Claims 23-25 employ the expression "or a prodrug or double prodrug thereof"

Claims 23-25 stand rejected on the ground that the expression "or a prodrug or double prodrug thereof" is indefinite. Although the action does not so state, it is believed that this

rejection was also meant to apply to claim 26. To overcome this ground of rejection, the expression in question has been deleted from claims 23-26 by amendment.

It should be noted that compounds (a)-(f) of claim 23 correspond to compounds (e),(f),(g), (h),(l) and (m) of canceled claim 6, and compound (g) of claim 23 corresponds to the compound of canceled claim9. Similarly, the compounds of claims 24, 25 and 26 correspond, respectively, to the compounds of canceled claims 8, 9 and 10. In Paper No. 5 (on page 2) the Examiner stated that these compounds had been examined and found allowable. Accordingly, now that the above-noted ground of rejection against claims 23-25 (and 26?) has been overcome by the above-mentioned amendment, these claims should be allowable.

3. Claims 26-28 are incomplete entities

The action states "Claims 26-28 are incomplete entities and cannot exist if made independent. They must rely on a proper independent claim." This basis for rejection is, respectfully, not understood, and clarification is requested. It is noted that claim 26 is directed to a single, specific chemical compound, or a physiologically acceptable salt thereof. As such, claim 26 can surely function as an independent claim. The rejection of claim 27 is rendered moot because this claim has been cancelled. Claim 28 does depend from a proper independent claim (claim 18), as well as from claims 19-26.

Rejections under 35 U.S.C. §112 (first paragraph)

Claims 29-33 are rejected under 35 U.S.C. §112 (first paragraph) for several distinct reasons. Each such reason is discussed below.

1. Claim 29 is rejected because the term "prevent", as it pertains to venous or arterial thrombotic disease, is asserted to not be believable on its face. The term is asserted to connote preventing the aging process. Although applicants would disagree with the stated ground of rejection, the claim has nonetheless been amended in an attempt to advance prosecution. As amended the claim reads on the prophylaxis or treatment of venous and arterial thrombotic disease. It is clear that the prophylaxis of thrombotic disease is believable on its face. It is well established that a great many drugs can be used for the prophylaxis of thrombotic disease. For example, the Examiner's attention is directed to the enclosed FDA-approved labeling for for the drug coumadin, which states that this drug is indicated for "the

prophylaxis and/or treatment of venous thrombosis". Use of the term "prophylaxis" does not introduce new matter as it means essentially the same thing as prevention.

2. Claims 30-31 are rejected for the same reasons advanced with respect to claim 29. It is respectfully urged that the rejection of claim 30, which depends from claim 29, is overcome by the amendment of claim 29, for the reasons expressed above with respect to claim 29. It is respectfully asserted that the stated ground of rejection is not applicable to claim 31. Claim 31 is directed to a method for providing antithrombotic support in thrombotic treatment utilizing rt-PA or streptokinase. Thus, claim 31 is essentially directed to a method for enhancing the antithrombotic effect of either rt-PA or streptokinase, two well-recognized antithrombotic agents, in which method an antithrombotic agent according to the present invention is also administered. There is nothing even remotely unbelievable in the assertion that administration of an antithrombotic agent in accordance with the invention would enhance the effect of another, well-recognized antithrombotic agent.

3. The rejections of claims 32 and 33 are rendered moot by their cancellation.

Amendments not necessitated by rejections

To improve clarity, the definition of the moiety R_2 has been amended in each of claims 18-22 in the following manner:

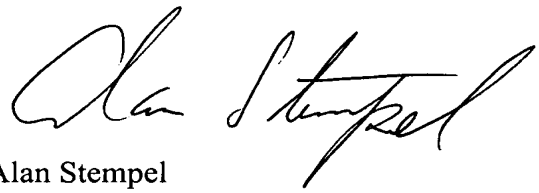
> R_2 denotes ***, or
>
> a C_{2-4}-alkyl group substituted, at a carbon which is other the one in the α-position relative to the adjacent nitrogen atom, by a hydroxy *** group,
>
> [whilst in the abovementioned groups the carbon atom in the α-position relative to the adjacent nitrogen atom may not be substituted,]

No substantive change, and hence no new matter, is introduced by this amendment.

Conclusion

It is earnestly asserted that all rejections have been overcome or rendered moot by the amendments made herein. It is thus urged that all claims now pending are allowable and that the application as a whole is now in condition for allowance.

Respectfully submitted,



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Enclosure: Copy of package insert (instructions for use) for coumadin

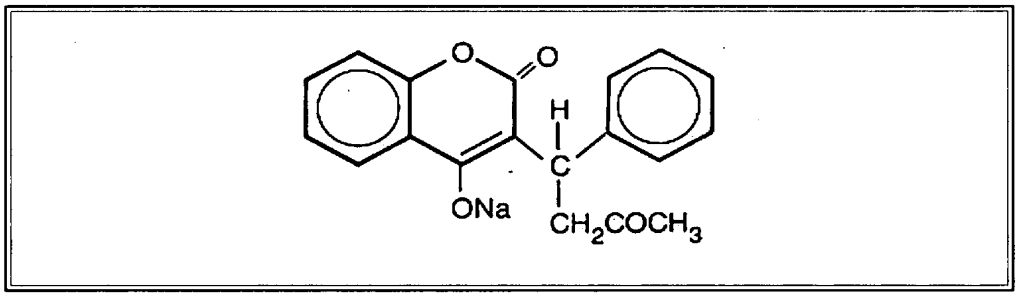
#10 Attach

Report generated 01/12/2000 at 10:26 am

COUMADIN FOR INJECTION (DUPONT PHARMACEUTICALS COMPANY)

DESCRIPTION

COUMADIN (crystalline warfarin sodium), is an anticoagulant which acts by inhibiting vitamin K-dependent coagulation factors. Chemically, it is 3-((alpha)-acetonylbenzyl)-4-hydroxycoumarin and is a racemic mixture of the R and S enantiomers. Crystalline warfarin sodium is an isopropanol clathrate. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin. Its empirical formula is $C_{19}H_{15}NaO_4$ and its structural formula may be represented by the following:



Crystalline warfarin sodium occurs as a white, odorless, crystalline powder, is discolored by light and is very soluble in water; freely soluble in alcohol; very slightly soluble in chloroform and in ether.

COUMADIN Tablets for oral use also contain:

All strengths:	Lactose, starch and magnesium stearate
1 mg:	D&C Red No. 6 Barium Lake
2 mg:	FD&C Blue No. 2 Aluminum Lake and FD&C Red No. 40 Aluminum Lake
2 1/2 mg:	D&C Yellow No. 10 Aluminum Lake and FD&C Blue No. 1 Aluminum Lake
3 mg:	FD&C Yellow No. 6 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake and FD&C Red No. 40 Aluminum Lake
4 mg:	FD&C Blue No. 1 Aluminum Lake
5 mg:	FD&C Yellow No. 6 Aluminum Lake
6 mg:	FD&C Yellow No. 6 Aluminum Lake and FD&C Blue No. 1 Aluminum Lake
7 1/2 mg:	D&C Yellow No. 10 Aluminum Lake and FD&C Yellow No. 6 Aluminum Lake
10 mg:	Dye Free

COUMADIN for Injection is supplied as a sterile, lyophilized powder, which, after reconstitution with 2.7 mL sterile Water for Injection,